Fracture in the Elderly Multidisciplinary Rehabilitation III

A definitive randomised controlled trial and economic evaluation of a community-based Rehabilitation package following hip fracture.

Acronym: Fracture in the Elderly Multidisciplinary Rehabilitation - Phase III (FEMuR III)

FEMuR III Protocol v1.0 27/07/2018

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General Information
This document describes the FEMuR III trial including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. Essential trial documentation will be circulated to the registered investigators in the trial, but sites entering patients for the first time are advised to contact the coordinating site at The University of Liverpool, Clinical Trials Research Centre (CTRC) to confirm they have the most up to date versions. Clinical problems relating to this trial should be referred to the Chief Investigator, Nefyn Williams, via the CTRC.

This protocol defines the participant characteristics required for trial entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements and waivers to authorise non-compliance are not permitted. Incidence of protocol non-compliance, whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is located in section 12.

Relationship Statements
Roles and responsibilities are fully described in section 15.

The University of Liverpool is the Sponsoring organisation and will formally delegate specific sponsoring roles to the Chief Investigator and CTRC, but remains legally responsible for the trial.

The CTRC at the University of Liverpool in collaboration with the chief investigator, Professor Nefyn Williams, will have overall management responsibility for the trial from a CTRC perspective and will be responsible for the co-ordination of sites.

CTRC as part of the Liverpool Clinical Trials Collaborative has achieved full registration by the UK Clinical Research Collaboration (www.ukcrc.org) as their standards and systems were assessed by an international review panel as reaching the highest quality. The Liverpool CTRC has a diverse trial portfolio underpinned by methodological rigour, a GCP compliant data management system, and core standard operating procedures.

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The contact details of other individuals involved in the trial are detailed in documents supplementary to the protocol and stored in the Trial Master File:

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Trial Management Group (TMG) Trial Steering Committee (TSC) Independent Data and Safety Monitoring Committee (IDSMC)	Held in the FEMuR III Trial Master File
Principal Investigators	Held in the FEMuR III Trial Master FileSite

1 TABLE OF CONTENTS

Glossary

ADL	Activities of Daily Living
AE	Adverse Event
AMTS	Abbreviated Mental Test Score
CI	Chief Investigator
CRF	Case Report Form
CSRI	Client Service Receipt Inventory
CTRC	Clinical Trials Research Centre
CTU	Clinical Trials Unit
FES	Falls Efficacy Scale
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HRA	Health Research Authority
HTA	Health Technology Assessment
IDSMC	Independent Data Safety and Monitoring Committee
NEADL	Nottingham Extended Activities of Daily Living
NRES	National Research Ethics Service
NICE	National Institute of Health and Clinical Excellence
NIHR CRN	National Institute for Health Research Clinical Research Network
PI	Principal Investigator
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RN	Research Nurse (Registered)
RSI	Reference Safety Information
RSO	Research Support Office
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
VAS	Visual Analogue Scale

2 PROTOCOL SUMMARY

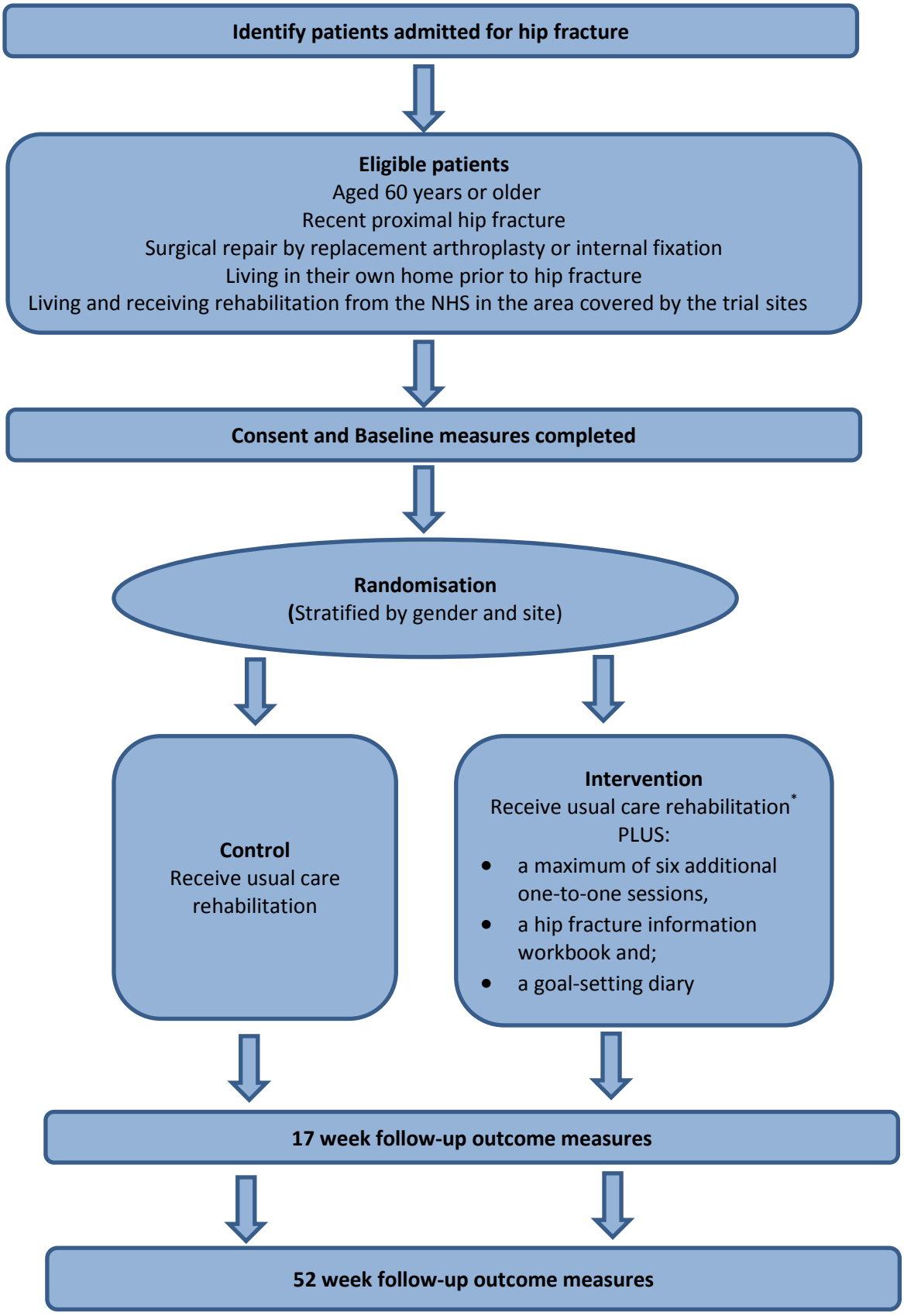
Full Title:	A definitive randomised controlled trial and economic evaluation of a community-based rehabilitation package following hip fracture.
Acronym	Fracture in the Elderly Multidisciplinary Rehabilitation - Phase III (FEMuR III)
Phase:	Definitive Phase III Randomised Controlled Trial with concurrent economic and process evaluations and an internal pilot phase.
Target Condition:	Older adults (aged ≥60) recovering from surgical treatment following hip fracture. The surgical repair will have been by replacement arthroplasty or internal fixation. They will have been living independently prior to fracture, have mental capacity (to be assessed by the clinical team) and will receive rehabilitation from the NHS in one of the areas covered by the trial sites. In addition we will attempt to recruit their informal and primary (familial) carers.
Sample size	446 patients N.B. Carers and therapists will also be asked to provide data (see Section 7 For more details)
Sub-group	Carers of patients recovering from hip fracture recruited for this trial will also be invited to take part in reporting their experiences of the type and level of support they give. Carers will be invited across both of the trial arms.
Main Inclusion Criteria :	1. Age 60 years or older 2. Recent proximal hip fracture including the following types of fracture: intracapsular, extracapsular (peri-trochanteric, inter-trochanteric, reverse oblique or sub-trochanteric) 3. Surgical repair by replacement arthroplasty or internal fixation 4. Living in their own home prior to hip fracture 5. Living and receiving rehabilitation from the NHS in the area covered by the trial sites
Main Exclusion Criteria :	• Living in residential or nursing homes prior to hip fracture • Participants who are not able to understand English or Welsh • Lacking mental capacity to give informed consent
Trial Sites and Distribution:	Patients will be recruited on orthopaedic and rehabilitation wards; intervention will be delivered in the community following hospital discharge. The trial will aim to open 12 sites in six regional sites (Merseyside, North Wales, South Wales, Nottingham, East Anglia and London).
Patient Trial Duration:	Rehabilitation intervention will be delivered in the 16 weeks following surgical repair of hip fracture. Patients will be followed up at 17 and 52 weeks post-surgery

Overall Trial duration	42 months	
Agent/ Intervention:	**Intervention:** Enhanced rehabilitation programme **Control:** Usual rehabilitation care	
	Objectives	**Outcome Measures**
Primary	To determine the effectiveness of an enhanced rehabilitation programme following surgical repair of proximal femoral fracture in older people compared with usual care, in terms of the performance of activities of daily living at 52 weeks follow-up.	Patient completed questionnaire using the Nottingham Extended Activities of Daily Living (NEADL) scale. Administered by blinded researchers at baseline, and after 52 weeks' follow-up.
Secondary	1. To compare the cost-effectiveness of an enhanced rehabilitation programme following surgical repair of proximal femoral fracture in older people compared with usual care, in terms of a cost-utility analysis from a health service and personal social care perspective.	Economic measures: EuroQol EQ-5D-3L and bespoke Client Service Receipt Inventory (CSRI) to capture patient service use.
	2. To determine the effectiveness of an enhanced rehabilitation programme following surgical repair of proximal femoral fracture in older people compared with usual care, in terms of the performance of activities of daily living at 17 weeks follow-up.	Patient completed questionnaire using the Nottingham Extended Activities of Daily Living (NEADL) scale. Administered by blinded researchers at baseline, and after 17 weeks' follow-up.
	3. To determine the effectiveness of an enhanced rehabilitation programme following surgical repair of proximal femoral fracture in older people compared with usual care, in terms of anxiety and depression at 17 and 52 weeks follow-up	Patient completed questionnaire using the Hospital Anxiety and Depression Scale (HADS). Administered by blinded researchers at baseline, and after 17 and 52 weeks' follow-up.

	4. To assess whether the enhanced rehabilitation intervention creates change in self-efficacy, hip pain, cognitive function, fear of falling and physical function as potential mediators for improving activities of daily living.	Patient completed questionnaire using the Falls Self-efficacy – International scale, Visual Analogue Score (VAS) for hip pain intensity, VAS for fear of falling, Abbreviated Mental Test Score (AMTS) at baseline and after 17 and 52 weeks. Patient completed physical function test: grip strength Administered by blinded researchers at baseline, and after 17 and 52 weeks' follow-up. Patient completed physical function tests: The short physical performance battery (SPPB). Administered by blinded researchers at 17 and 52 weeks' follow-up.
	5. To assess whether the enhanced rehabilitation intervention creates change in care-giver strain, anxiety and depression in carers.	Carer completed questionnaire using the Carer Strain Index (CSI), Hospital Anxiety and Depression Scale (HADS). Administered by blinded researchers at baseline, and after 17 and 52 weeks' follow-up.
	6. To determine the mechanisms and processes that explain the implementation and impacts of the enhanced rehabilitation programme	A process evaluation will include qualitative interviews of a purposive sample of participants in each of the two trial arms after the 17-week assessment and with therapists delivering the enhanced rehabilitation programme. We will also request routinely collected data that therapists complete on their information management systems. This will be sent to the qualitative researcher.

Protocol Summary - continued

Schematic of Trial Design:



* See section 8

3 INTRODUCTION

3.1 Background

Proximal femoral fracture, more commonly referred to as hip fracture, is a common, major health problem in old age. The total number of patients entered onto the national hip fracture database in England, Wales and Northern Ireland in 2015 was 65,645[1]. As the population ages the number of elderly people falling and fracturing their hips is projected to increase further[2,3]. Such fractures are strongly associated with decreased bone mineral density, increased age, prior fragility fracture, cognitive impairment, under-nutrition, frailty, poor physical functioning, vision problems, weight loss and other health problems[4]. Mortality is high with 14-58% dying within the following 12 months[5,6]. A review of the long-term disability associated with proximal femoral fracture found that 29% did not regain their level of functioning after one year in terms of restrictions of activities of daily living[7]. Many who were living independently before their fracture lost their independence afterwards. This imposes a large cost burden on society amounting to about £2.3 billion a year in the United Kingdom equating to approximately £6 million a day[8]. Tian et al.[9] explored Torbay's (Devon) unique patient-level linked data set of National Health Service (NHS) and social care costs for older people in the 12 months before and after being admitted to hospital as a result of a fall. They found that the cost of hospital, community and social care cost services for each patient were almost four times as costly in the 12 months after admission, compared with the costs of the admission itself, and that the majority of costs occurred outside of the acute hospital setting. Particularly frail individuals may go onto have a further proximal femoral fracture resulting in additional disability and deaths[10].

The National Institute of Health and Clinical Excellence (NICE) have issued guidelines for the management of hip fracture that include the provision of a co-ordinated multidisciplinary rehabilitation programme starting in hospital during post-operative recovery and continuing in the community following discharge[11]. NICE guidelines also state that where possible such rehabilitation programmes should consider individual patient goals, facilitate a return to pre-fracture independence and provide patients and carers with written information on the rehabilitation programme and long-term outcomes. NICE also calls for further evidence of cost-effectiveness of interventions for hip fracture management, as this is currently lacking in this field[11].

3.2 Rationale

There have been four relevant Cochrane systematic reviews with inconclusive results[12-15]. A review of different types and intensities of in-patient rehabilitation[12] found no statistically significant difference in mortality or hospital re-admission in a meta-analysis of 11 RCTs of in-patient rehabilitation. Individual RCTs found better results in the intervention group for activities of daily living. Two RCTs examined home-based rehabilitation. One found a marginal improvement in function and reduced carer burden for early discharge to home-based rehabilitation; the other found no difference between intensive and less intense rehabilitation. A review of mobilisation strategies[13] identified 12 small RCTs of early mobilisation strategies following surgery and seven of community interventions following hospital discharge. Results were mixed and it was concluded that it was possible to enhance mobility after hip fracture, but that the best method to do this was unclear. Psychological factors such as fear of falling, perceived control and coping strategies influence recovery following hip fracture[16-19]. A review of psychosocial functioning after hip fracture[14] identified nine small heterogeneous RCTs with inconclusive results. A review of rehabilitation for those with dementia following hip fracture surgery found five RCTs, but insufficient evidence[15]. Other systematic reviews have reported improved walking ability[20], strength and physical function[21], including those with mild to moderate dementia[22]. In the related area of rehabilitation following joint replacement for osteoarthritis, a systematic review found that post-operative self-efficacy was associated with recovery outcomes such as longer distance ambulation, exercise repetition and frequency, walking speed and disability[23]. Self-efficacy has been defined as the sense of competence a person holds with regards to carrying out general, or specific actions, as required by general or specific situations[24]. Overall, these systematic reviews concluded that whilst individual

components of rehabilitation programmes may aid recovery after a hip fracture, there was insufficient evidence to demonstrate overall clinical or cost-effectiveness of an overall care pathway, and that further research was required. These systematic reviews have not allowed an exploration of how and why an intervention led to a reported outcome. A different approach is to use a realist review which aims to elucidate the mechanism behind an intervention and to determine what works, for whom, in what circumstances and why? These are described in programme theories according to their context (C), mechanism (M) and outcome (O).

3.2.1 **Summary Phase I: Developing the Intervention**

A HTA funded trial[25] completed the first two phases of the MRC framework for complex interventions[26]. The first phase developed a coherent theoretical basis for the intervention from a realist review of the literature, a survey of current practice in the UK, and focus groups of the multi-disciplinary rehabilitation teams, hip fracture patients and their carers[27]. This resulted in the following overarching working theory:

"In the context of patients with a great range and variety of pre-fracture physical and mental comorbidities affecting their ability to meet rehabilitation goals, a tailored intervention incorporating increased amount of high quality practice of exercise and activities of daily living leads to better confidence, mood, function, mobility and reduced fear of falling."

There were three underlying programme theories:

1. Improve patient engagement by tailoring the intervention according to individual needs and preferences. "Elderly proximal hip fracture patients presenting with a range of pre-fracture physical and mental functioning and a variety of co-morbidities (C) need a rehabilitation programme that is tailored to individual needs (M) in order to achieve appropriate outcomes such as improved physical functioning, greater mobility, reduced disability and independent living (O)."

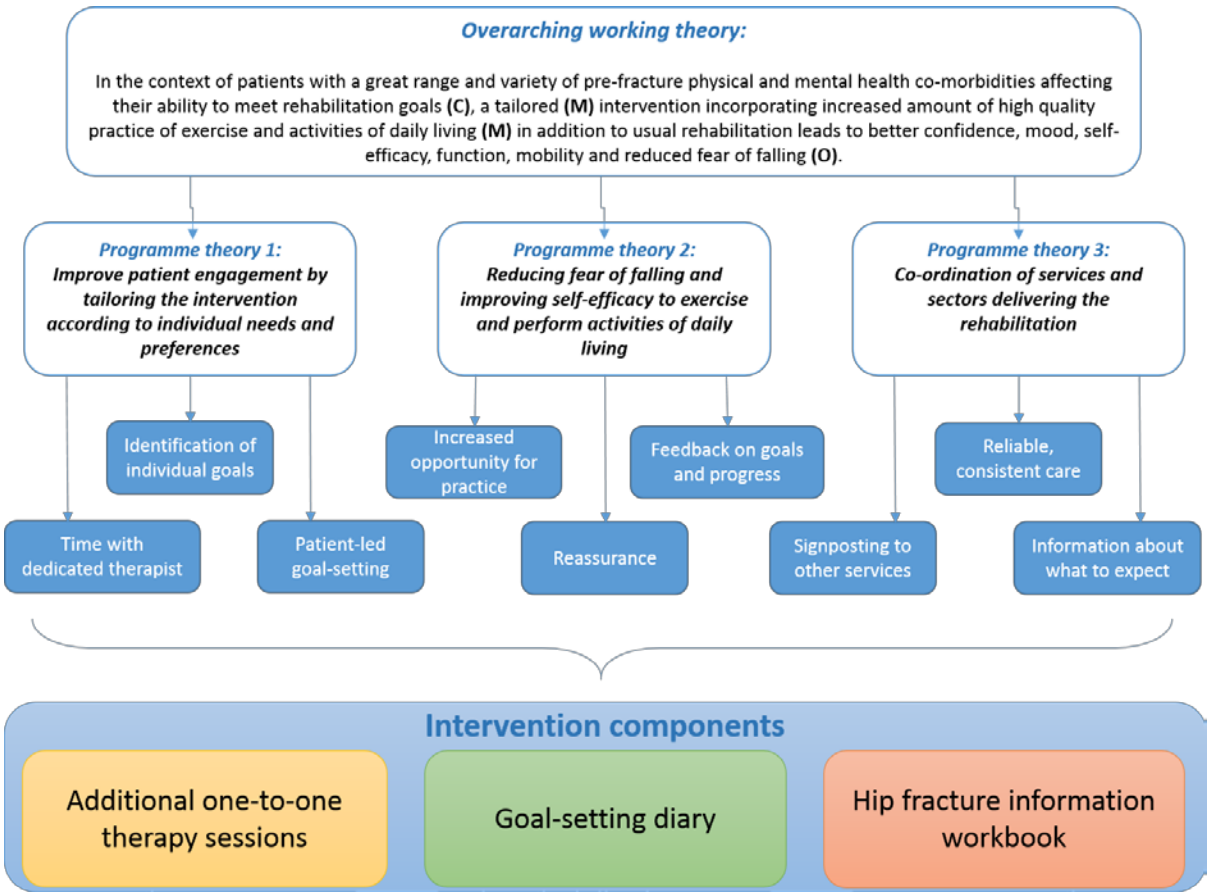
2. Reduce fear of falling and improve self-efficacy to exercise and perform activities of daily living. "Proximal hip fracture results in poor physical functioning, fear of falling, low mood and lack of self-efficacy (C) requiring improved quality and increased amount of practice of physical exercises, activities of daily living and psychological tasks (M) in order to gain mastery and control to improve confidence, mobility and physical functioning (O)."

3. Co-ordination of services and sectors delivering the rehabilitation.
"The diversity of services provided by different disciplines, across sectors from a variety of funders (C) requires a co-ordinated provision of the multidisciplinary rehabilitation programme (M) in order to deliver appropriate physical, functional and psychological interventions to patients in a timely manner (O)."

These theories were then used to inform the development of a co-ordinated complex intervention consisting of physical and psychological components (see figure 1 below):

1. Six home-based therapy sessions delivered by physiotherapists or occupational therapists with the assistance of a technical instructor providing reliable and consistent care.
2. A novel, patient-held, workbook containing information on hip fracture, what to expect from rehabilitation, importance of physical activity and maintaining functional activities and signposting to other services available.
3. A diary to facilitate patient-led goal-setting, promote engagement and increase self-management.

Figure 1 Development of the intervention from programme theories



3.2.2 Summary of Phase II Methods

The second phase of the trial assessed the feasibility and acceptability of the intervention; the enhanced rehabilitation package (intervention components outlined in figure 1) in a cohort study of all hip fracture patients with an embedded randomised feasibility trial and further focus groups of rehabilitation teams, patients and carers[28]. This trial assessed the feasibility of methods for a future definitive parallel-group randomised controlled trial (RCT) and economic evaluation. Participants in the feasibility trial were recruited from three acute hospitals in North Wales, and the rehabilitation intervention was delivered in the community. Participants were older adults aged 65 years or older who had received surgical treatment for hip fracture, had been living independently prior to the hip fracture, had mental capacity as assessed by their clinical team, and received rehabilitation in the North Wales area. Participants were randomised using a remote method to usual care (control) or usual care plus the enhanced rehabilitation package (intervention), which included up to six additional home-based physiotherapy sessions delivered by a physiotherapist or technical instructor, a novel information workbook and a goal-setting diary. For this feasibility trial, the primary outcome measure was the Barthel Activities of Daily Living scale (BADL). Secondary measures included: the Nottingham Extended Activities of Daily Living scale (NEADL), EuroQol EQ-5D, ICECAP capability, Hospital Anxiety and Depression Scale (HADS), visual analogue scale for hip pain intensity, General Self-Efficacy Scale, Falls Efficacy Scale – International (FES-I), Self-Efficacy for Exercise scale, visual analogue scale for fear of falling, tests of physical function and the Clinical Service Receipt Inventory. Outcome measures were assessed at baseline and 3-month follow-up by blinded researchers.

3.2.3 **Summary of Phase II Results**

3.2.3.1 Randomised Feasibility Trial[29]

Between June 2014 and March 2015, 593 patients with proximal femoral fracture were screened for eligibility, of which 266 (45%) were eligible. The main reason for ineligibility was lack of mental capacity (49%). Out of those eligible 193 (73%) were invited to participate and 62 (23% of the eligible population) agreed to participate. The main reason for non-participation was the perceived burden of the trial. From the recruited participants 41 carers were identified with 31 agreeing to participate (76%).

The two groups were similar with regard to age, gender, living status, type of property, type of fracture, type of surgery and admitting hospital. The baseline scores of the outcome measures and physical function tests were similar between the two groups; however the NEADL scale was 2.4 points higher in the control group (indicating better functioning).

There were nine withdrawals, one before baseline and eight during the intervention (four from each group). Four patients could not be contacted at follow-up, resulting in a patient retention rate of 79% overall (intervention group 86%; control group 75%). Six of the carers withdrew during the trial and seven were lost to follow-up and only 18 completed the follow-up questionnaire; a carer retention rate of 44%.

At three-month follow-up there were minimal differences between the two groups for most of the outcome measures, including the main outcome measure the BADL index, with an adjusted mean difference of 0.5 (Cohen's d=0.29), but there was a trend for a greater improvement in the intervention group, but with small effect sizes. However, the NEADL showed a medium effect size, also in favour of the intervention group, with an adjusted mean difference of 15.8 (Cohen's d=0.63). On the other hand, in the physical function tests the 'fifty-feet walk test' was completed in a shorter time in the control group with a medium effect size, with an adjusted mean difference of 12.2 seconds (Cohen's d=0.40). This might be explained by the control group completing these physical function tests three weeks later than the intervention group.

The economic evaluation used a cost consequence analysis. The cost of delivering the intervention was £231 per patient. Both the intervention and control groups showed improvements in EQ-5D health utility index scores and the ICECAP capability index scores from baseline to the three-month follow-up. The differences between groups were not statistically significant, but this small feasibility trial was not powered to test such differences. The intervention group had slightly higher mean QALY gains than the control group, which were not statistically significant either. The difference in QALY was 0.02 (95% CI -0.02 to 0.06). There was however, a statistically significant difference in hospital costs between the groups due to longer inpatient stays in one group. The mean total service use costs were £43 999 higher in the intervention group (95% CI £4 027 to £88 818).

3.2.3.2 Cohort Study

Four hundred proximal femoral fracture patients were recruited to the anonymised cohort study. When they were compared with those in the feasibility trial, the proportions were similar with regard to gender, type of hip fracture and surgery. However, the cohort population was slightly older (mean age difference of 4.5 years), more likely to be re-admitted to hospital and more likely to die.

3.2.3.3 Focus groups

The key findings were that in the context of variable usual rehabilitation care, the role of the therapist was extremely important in managing patients' needs and expectations. This was especially so at the beginning of rehabilitation, for giving permission about what physical activity was safe to do. Regular home visits allowed a relationship to build between patient and rehabilitation therapist, which was important for patient engagement. Patients valued the use of tailored care and

personal goal-setting as a motivational tool. These activities were well supported by the workbook and the goal-setting diary.

3.2.4 **Recommendations for the Phase III definitive RCT**

In conclusion, the phase II trial found that the trial methods for a full definitive RCT and economic evaluation were satisfactory. In particular, there were suitable rates of eligibility, recruitment, retention and outcome measure completion. The enhanced rehabilitation package was acceptable to patients, carers and therapists. There was variability in usual care, which resulted in some in the control group receiving no rehabilitation in the community at all. In addition to enhancing self-efficacy and promoting personal goal-setting and self-monitoring, the enhanced rehabilitation package provided a minimum set of therapy sessions no matter what was provided with usual care. The most suitable outcome measures for a definitive RCT are the NEADL scale as the primary effectiveness outcome; the EuroQol EQ-5D as the primary health economic outcome; and the FES-I for measuring self-efficacy. The results of the feasibility trial informed a sample size calculation for this proposal.

3.2.5 **Risk and Benefits**

Systematic reviews have concluded that whilst individual components of rehabilitation programmes may aid recovery after a hip fracture, there was insufficient evidence to demonstrate overall clinical or cost-effectiveness of an overall care pathway. An enhanced rehabilitation package was developed and tested it in a phase II feasibility trial and although this trial was under-powered to assess statistical significance, it had a medium sized effect on the NEADL scale. The risks of the two interventions are minimal however there may be a risk of injury or falling when performing the therapeutic exercise; however this risk will be mitigated by the supervision of qualified therapists and technical instructors. From the feasibility trial, the supervision of rehabilitation by qualified therapists varied greatly between participants according to local circumstances for example some participants did not receive any community-based rehabilitation at all, instead only receiving hospital based rehabilitation and information on discharge. The enhanced rehabilitation package is low risk as it consists of a workbook to improve self-efficacy, a goal-setting diary and up-to six additional therapy sessions.

Participants randomised to the intervention arm will have more access to a health care professional than they would in normal care, beyond this there are no other known benefits to this trial.

3.3 Objectives

3.3.1 **Primary Objective**

The primary objective is to determine the effectiveness of an enhanced rehabilitation programme following surgical repair of proximal femoral fracture in older people compared with usual care, in terms of the performance of activities of daily living at 52 weeks follow-up.

3.3.2 **Secondary Objective(s)**

1. To compare the cost-effectiveness of an enhanced rehabilitation programme following surgical repair of proximal femoral fracture in older people compared with usual care, in terms of a cost-utility analysis from a health service and personal social care perspective.

2. To determine the effectiveness of an enhanced rehabilitation programme following surgical repair of proximal femoral fracture in older people compared with usual care, in terms of the performance of activities of daily living at 17 weeks follow-up.

3. To determine the effectiveness of an enhanced rehabilitation package following surgical repair of proximal femoral fracture in older people compared with usual care, in terms of anxiety and depression at 17 and 52 weeks follow-up.

4. To assess whether the enhanced rehabilitation intervention creates change in self-efficacy, hip pain, cognitive function, fear of falling and physical function as potential mediators for improving activities of daily living.

5. To assess whether the enhanced rehabilitation intervention creates change in care-giver strain, anxiety and depression in carers.

6. To determine the mechanisms and processes that explains the implementation and impacts of the enhanced rehabilitation programme.

3.4 Outcome measures/endpoints

Each measure to be used for the outcomes described in this protocol has been chosen due to their recognised use with patients in measuring physical and mental health status. Each measure is either validated or researched for use.

Routinely collected data will be used to collect information about demographics. Participants' cognitive function will be assessed using the Abbreviated Mental Test Score (AMTS)[33]. At baseline, 17 and 52 weeks outcome measures will be completed by participants with assistance from a member of the research team blinded to participant allocation. Objective measurement of physical function will be assessed by the researcher at baseline, 17 weeks and 52 weeks using the grip strength test. At 17 and 52 weeks follow up, a researcher will measure physical function using the Short Physical Performance Battery (SPPB) of tests in the patient's home. Qualitative interviews will take place with patient's carers after 17 weeks to gather feedback on trial participation and intervention design.

3.4.1 **Primary Outcome/Endpoint**

The primary outcome measure will be of the difference in performance of activities of daily living at 12 months follow-up,, between the usual rehabilitation arm and the enhanced rehabilitation arm using the NEADL Scale

3.4.2 **Secondary Outcome/Endpoints**

Secondary endpoints include:

Efficacy:

1. Anxiety and depression (HADS) [36]
2. Cognitive status (AMTS)[33]
3. Hip pain intensity at (VAS) for hip pain intensity[37]
4. Falls self-efficacy (FES-I) (self-efficacy)[38,39]
5. Fear of falling (VASFoF)[40]
6. Physical function (SPPB)[49,50]
7. Grip strength[46]

Carer behaviours may make an important contribution to the intervention's effectiveness. We will also include items to measure care tasks and roles in terms of the type of support provided and the number of hours spent providing support. We will ask about help with the workbook, goal-setting and the practice of rehabilitation exercises as well as more general assistance.

Carer of patient:

8. Care-giver strain (CSI)[51]
9. Care-giver anxiety and depression(HADS)[36]

Safety:

10. Number of adverse events across the two arms
11. Number of serious adverse events across the two arms
12. Number of re-admissions to hospital following hip-fracture repair surgery

Health Economics:

13. Incremental cost-utility ratios, EuroQol EQ-5D-3L (three levels)[41]
14. Health service and personal social care Cost-utility, (CSRI)[43]

Process Evaluation:

15. Refine the programme theory that was generated from the previous realist review when developing the intervention programme
16. Investigate therapists' expectations and experience of implementation, identifying the actual practices, likely tailoring and interactions that took place within the trial setting. Also, investigate therapists' skill level, relevant training, previous experience and level of familiarity of working in this sector. Finally, investigate therapists learning over time and its potential impact on outcomes.
17. Investigate the mechanisms driving and shaping the tailoring of the enhanced rehabilitation programme to individual patients and its possible impacts on outcomes.
18. Investigate trial participants' experiences and views about their involvement in the FEMuR trial.
19. Synthesize all data collected and link it to the explanation of trial findings in relation to the refined programme theory.

3.4.3 **Routinely collected demographic, clinical and recruitment data**

1. The number of eligible patients who fulfil the inclusion criteria
2. The number who are willing to be randomised
3. The number who withdraw after baseline assessment and randomisation
4. The number who complete the various outcome measurements at baseline and follow up.
5. The researchers who administer the outcome measures will record the reasons for any non-completion.
6. Date of birth (age)
7. Gender
8. Type of hip fracture
9. Type of surgery
10. Living arrangements
11. Important co-morbid conditions
12. Place of residence prior to admission
13. Place of discharge from acute and/or community hospital

4 TRIAL DESIGN

This is a pragmatic multisite randomised controlled trial (RCT). This will be a parallel-group, two-armed, superiority RCT, with 1:1 allocation ratio, stratified by gender and site. The experiences in a Phase II randomisation feasibility trial (section 3.2.3) have been used to inform the design of this trial and furthermore there is an internal pilot phase to assess trial feasibility (section 4.1). Blinded outcome assessment and statistical analysis; unblinded patient and carer participants and clinicians. Economic evaluation will be a cost-utility analysis from a health service and personal social care perspective.

An internal pilot will assess recruitment and retention for the 6 months after the first site has been opened to recruitment. Results from the phase II feasibility trial found that the rate of recruitment for those eligible and invited to participate was 32% (95% CI 26 to 39%), and retention rate was 79% (95% CI 69 to 89%). The monthly recruitment target per site will be 3.25 participants (again based on the feasibility trial recruitment rates).

The progression criteria from the internal pilot phase to the main trial will be in terms of stop, amend or go. All progression criteria should be met or amended as needed before progression to the main trial. The progression criteria are as follows:

Progression Criteria	**Go**	**Amend**	**Stop**
Sites open	7 sites or more	5-6 sites	4 sites or fewer
Open site recruitment rate per month	2 or more participants	1-2 participants	Fewer than 1 participant
Retention rate*	69% or higher	50-68%	49% or lower

* Rates will be rounded to the nearest whole number before applying the progression criteria

5 TRIAL SETTING AND SELECTION OF SITES / CLINICIANS

Patients will be recruited in secondary care on orthopaedic and rehabilitation wards of approximately 12 acute hospital sites, and follow up and delivery of intervention will occur in their associated community hospitals. The intervention will be delivered in the community, following hospital discharge, by community teams receiving referrals from the acute hospital sites and their associated community hospitals.

5.1 Selection of Sites/Clinicians

There are lead applicants from six university sites: Liverpool, Bangor, Cardiff, Nottingham, Oxford and King's College London. Each lead applicant has identified two NHS sites each with the aim of opening approximately 12 sites in total. If additional sites are needed in the future, criteria for the selection of sites will be determined by the TMG using site feasibility criteria.

Initiation of sites will be undertaken in compliance with CTRC SOPs. Sites fulfilling the feasibility criteria will be selected to be recruitment sites for the FEMuR III trial and will be opened to recruitment upon successful completion of all global (ethical and governance) and trial-specific conditions (e.g. site personnel training requirements) and once all necessary documents have been returned to CTRC as detailed in the trial 'greenlight' checklist.

The site trial team is likely to comprise of the Principal Investigator, ward clinical staff, community clinical staff and the Research Project Support Officer (RPSO) with support also from the research delivery team of the clinical research network (CRN) in England, or the health board's research and delivery department in Wales.

6 TRIAL POPULATION

6.1 Inclusion Criteria

1. Age 60 years or older
2. Recent proximal hip fracture including the following types of fracture examples: intracapsular, extracapsular (peri-trochanteric, inter-trochanteric, reverse oblique or sub-trochanteric)
3. Surgical repair by replacement arthroplasty, hemiarthroplasty or internal fixation
4. Living in their own home prior to hip fracture
5. Living and receiving rehabilitation from the NHS in the area covered by the trial sites

6.2 Exclusion Criteria

1. Living in residential or nursing homes prior to hip fracture
2. Participants who are not able to understand English or Welsh
3. Lacking mental capacity to give informed consent

6.3 Co-enrolment Guidelines

To avoid potentially confounding issues, ideally patients should not be recruited into other trials during their participation in FEMuR III. Where recruitment into another trial is considered to be appropriate and without having any detrimental effect on the FEMuR III trial, this must first be discussed with the CTRC who will contact the Chief Investigator (Professor Nefyn H Williams).

7 RECRUITMENT AND RANDOMISATION

This trial will recruit hip fracture patients (hereafter referred to as “patient participants” and additionally their carers (hereafter referred to as “carer participants”). Carer participants will provide informed consent similarly to patient participants (see sections 7.2 to 7.3) but will not receive any trial intervention so will not undergo eligibility screening (section 7.4) or randomisation (section 7.6)

7.1 Participant Identification and Screening

A screening log of patients who are assessed for eligibility but not randomised will be maintained as this will provide important information for monitoring purposes. Reasons for not being eligible and timelines for providing information and approaching the patient for consent will be recorded. Reasons for declining to participate will be asked routinely but it will be made clear that patients do not have to provide a reason unless happy to do so. Copies of the completed screening log should be sent to CTRC every 4 weeks or when requested.

Patients will be reviewed whilst recovering from surgical repair on an orthopaedic or a rehabilitation ward or occasionally after discharge home. Those patients who meet the criteria will be suitable for inclusion (section 6.1 and 6.2) and will be provided with information about the trial, (both verbal and written) to see if they would be interested in taking part and willing to be seen by a researcher. Each potential participant will be approached when the clinical team believe that it is appropriate according to individual circumstances. Assessment of eligibility may occur over an extended period of time or in a different location to the orthopaedic ward, if for example, the patient is experiencing temporary delirium post-surgery (section 7.4).

Prior to any trial-specific procedures or assessments or randomisation being performed, full eligibility of each patient must be confirmed by a member of the research team listed on the delegation log with this duty. Only those authorised on the site Delegation Log can confirm full eligibility of any patient; a record of this confirmation must be made in the patient’s medical notes on the date of screening.

Carers, for the purpose of this trial, are defined as a relative or friend caring for a hip fracture patient recruited to the trial, by providing them with face-to-face support most days (at least four out of seven) in a week including help with activities of daily living or physical care. The trial site researchers will also seek to identify and recruit carers. Whilst carer participation is desirable, patient participant informed consent should be obtained as a priority for this trial.

7.2 Informed Consent

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual’s participation. Informed consent is required for all individuals participating in CTRC coordinated trials. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

In Wales, Welsh versions of the Patient Information and Consent Forms (PISC) will be available. Patient and carer participants will be given ample time to decide whether to join the trial or not but should be randomised within 4 weeks of hip fracture repair surgery. Participants who are not able to decide in this time will not be able to take part. Participants will be asked to sign one of the following consent forms:

- FEMuR III patient participant informed consent form (English)
- FEMuR III patient participant informed consent form (Welsh)
- FEMuR III carer participant informed consent form (English)

- FEMuR III carer participant informed consent form (Welsh)

Potential participants will be introduced to the trial and given a participant information sheet and consent form (PISC). Potential participants with mild dementia and cognitive impairment will be included, so long as they maintain the mental capacity to give informed consent. It will not depend upon the Abbreviated Mental Test Score, which is being used as an outcome measure for cognitive functioning. The capacity of patients to give informed consent will be decided by clinical staff on the orthopaedic wards. If however, potential participants score low on this score (8 or less) during follow-up, the researchers should then inform the PI and a clinician will be asked to reassess mental capacity and no further trial information can be collected until a PI or delegated other can confirm patient has capacity. Some potential participants will lack capacity because of a post-surgery temporary delirium. These people will be monitored closely and may need repeat visits from the research network staff until the temporary delirium has settled in order to obtain informed consent. These repeat visits may need to follow the potential participant after they have been discharged from the acute orthopaedic ward onto another ward, or another hospital, or after they have been discharged home.

7.3 Obtaining informed consent

Site staff delegated by the Principal Investigator (PI) and appropriately trained with experience in obtaining informed consent will conduct an interview with the patient and/or carer. The appropriate ethically approved Patient Information Sheet and Consent form (PISC) will also be provided, describing in detail the trial interventions, trial procedures and risks. The potential participant will be asked to read and review the document and upon reviewing the document, the investigator or delegated researcher will explain the research trial to the potential participant. A discussion of the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted will be provided to potential participants by staff with experience in obtaining informed consent. This information will emphasise that participation in the trial is voluntary and that the potential participant may withdraw from the trial at any time and for any reason. All potential participants will be given an opportunity to ask any questions that may arise and should have the opportunity to discuss the trial with their friends, family or carers with sufficient time to consider the information prior to agreeing to participate. Contact information, will be provided to participants where further information about the trial may be obtained.

If happy to participate, the participants will then sign and date the appropriate PISC. Both the researcher obtaining consent and the participant must personally sign and date the form. If the participant cannot sign the form for any reason such as poor eyesight or poor grip strength then a witness should be asked to sign the consent form, the participant should still try and sign and date the form as best as they can if possible. The original signed PISC must be filed in the site's Investigator Site File and three copies must be made: a copy placed in the participant's medical notes, a copy provided to the participant for their own records, and a copy returned to the CTRC. The original signed PISC for the carer participant should be filed in the investigator site file and a copy given to the carer participant. A note should be made in the patient participant medical notes detailing that consent has been obtained from a carer.

The rights and welfare of all participants will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this trial. The patient may, without being subject to any resulting detriment, withdraw from the trial at any time by revoking the informed consent. If a participant does not wish to continue in the trial the details should be entered into the eCRF.

The rights of the potential participants to refuse consent to participate in the trial, without giving a reason must be respected. After the patient participant has entered the trial, the clinician is free to give alternative intervention to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the patient participant. However, the reason for doing so should be recorded and the patient participant will remain within the trial for the purpose of follow-up and data analysis according

to the intervention option to which they have been allocated. Similarly, the patient participant remains free to withdraw at any time from the trial intervention and trial follow-up without giving reasons and without prejudicing their further treatment. If the patient participant withdraws from the trial we will continue follow-up assessments of any carer participants unless they also withdraw. If the carer participant withdraws we will continue follow-up assessments of the patient unless they also withdraw.

7.3.1 Patient participants

Patients will be approached, consented and randomised within 4 weeks of surgery. The clinical and research network staff should take into account the state of the patient's physical and mental health when approaching the patients. The assessment of mental capacity will be performed by clinical staff in the acute hospital as part of the eligibility assessment. It is anticipated that, the majority of patients may need two visits for their recruitment. If the patient is not yet ready to consent before hospital discharge, and wants more time to consider, we will request to contact the patient following discharge, but within the aforementioned timescales. Appropriately GCP trained and delegated research nurses or a research project support officer will obtain the informed consent. Patients will be given as long as required to decide whether to join the trial or not but a decision will need to be made prior to the patient being randomised. Randomisation should take place no later than 4 weeks after hip fracture repair surgery; if patient participants take longer than 4 weeks to decide, they will not be able to take part in the trial.

In order for a purposive sample of patients to be identified to take part in qualitative interviews, patients will also be asked to consent to being contacted for a telephone interview after their 17 week follow-up. Consent for this will be collected on the main trial PISC form. Patients will be asked to provide their contact details and consent will be re-affirmed prior to the semi-structured telephone interview.

7.3.2 **Carer participants**

The site trial team will identify and recruit carers (as defined in 7.1) following the trial's informed consent process. Carers will be given long as required to decide whether to take part in the completion of trial questionnaires. Carers will be asked to complete the CSII and HADS at baseline and at 17 and 52 week follow-up.

Whilst carers who decide to take part in the trial are not included as part of the trial sample group and will not be randomised to receive an intervention, the same principles of informed consent will apply.

In order for a purposive sample of carers to be identified to take part in qualitative interviews, carers will also be asked to consent to being contacted for a telephone interview after the 17 week assessment. Consent for this will be collected on the main trial carer PISC form. Carers will be asked to provide their contact details and consent will be re-affirmed prior to the semi-structured telephone interview.

7.4 Eligibility confirmation

Once a patient has been screened and has had all eligibility assessments performed and Informed Consent has been obtained, a clinician or delegated other authorised on the site Delegation Log must confirm full eligibility of the patient. A record of this confirmation must be made in the patients' medical notes on the date of screening.

7.5 Baseline

Informed consent must be obtained before baseline as trial-specific data are required as part of baseline assessment.

Once the patient (or witness) has provided written informed consent and a clinician or delegated other authorised on the trial site Delegation Log has confirmed full eligibility, the baseline assessments will be undertaken.

The researcher will record baseline process and outcome measures detailed in section 9.

7.6 Randomisation Procedures

Participants will be randomised by a delegated member of the research team. The randomisation will have an allocation ratio of 1:1 within each stratum and across the trial. Participants will be stratified by: (1) site and (2) gender. Randomisation is completed by secure web access to the remote randomisation site at the CTRC.

Participants will be randomised to receive either the enhanced rehabilitation intervention or usual rehabilitation care (in a ratio of 1:1) once:

a. Eligibility criteria have been confirmed;
b. Fully informed written consent has been obtained;
c. Baseline assessments have been completed.

A personal login username and password, provided by the CTRC, will be required to access the randomisation system; designated research staff will be issued with their personal login and password.

When the system requirements (eligibility, consent, and baseline assessment) are confirmed, the participant treatment allocation and a unique trial number will be displayed on a secure webpage and an automated email confirmation will be sent to the authorised randomiser, Principal Investigator (PI) and trial coordinator. A blinded copy of the randomisation email may also be sent to the relevant RPSO.

Randomisation: web access http://ctrc.liv.ac.uk/Randomisation/Femur3

If there are any problems with the randomisation systems contact the coordinating CTU on 0151 795 8764 or via email on femur3@liverpool.ac.uk

(Note that the coordinating CTU is open from 0900 – 1700, Monday – Friday, excluding public holidays)

In the event of a randomisation system failure, the site should contact the coordinating team in CTRC (Monday to Friday between 9:00 to 17:00 excluding bank holidays) to try to resolve the problem. If the problem cannot be resolved, the coordinating CTRC will perform central randomisation and randomise the participant using the back-up randomisation system or advise the site to randomise when the randomisation system is live. The back-up randomisation system is an exact replica of the live system but is based on a standalone PC at CTU.

8 TRIAL TREATMENT/INTERVENTIONS

8.1 Introduction

We plan to compare an enhanced rehabilitation intervention with usual rehabilitation care.

8.2 Usual rehabilitation care

Usual care consists of a multi-disciplinary rehabilitation delivered by the acute hospital, community hospital and community services depending on patients' individual needs at different times during their recovery and on the availability and accessibility of services in different areas. The multidisciplinary team delivering care and rehabilitation may include at different times: orthopaedic surgeons, orthogeriatricians, nurses, physiotherapists, occupational therapists, dieticians, pharmacists, GPs and social workers. The settings for care include acute orthopaedic or orthogeriatric wards, rehabilitation units in community hospitals, rehabilitation beds in care homes, the patient's own home and care home settings all delivered by a variety of community teams in both health and social care services. The findings from the Phase II feasibility trial were that the provision of usual community-based care was very variable, with some participants in the control group not receiving any community rehabilitation at all.

8.3 Enhanced rehabilitation

The main aim of the intervention is to enhance usual rehabilitation by enhancing patients' self-efficacy, and increasing the amount and quality of patients' practice of physical exercise and activities of daily living in order to improve their functional outcomes at 17 and 52 week follow up [24]. Self-efficacy will be enhanced by means of a patient held information workbook and diary given to the participant in the acute hospital and kept with them throughout the follow up period of the trial. In addition to whatever community based rehabilitation is provided as part of usual care, we will provide up to six additional therapist (physiotherapist or occupational therapist) or technical instructor sessions to patients once they either return home or are admitted permanently to a care home. The extra sessions will be tailored by the therapists delivering them, and so the total number of sessions used, the time scale for their delivery, and the sessions' content will vary between patients according to clinical need.
The workbook will also include information about what to expect from their recovery and information about NHS, council and voluntary sector services they may be able to use. This will include a variety of community services such as falls preventions programmes. The objectives of the workbook and diary are to:

1) Give patients better understanding of what has happened physically to them and to broadly outline what to expect during their recovery.
2) Provide information and contact details on rehabilitation services that are available to them as they progress in their rehabilitation (e.g. Intermediate care teams, social services enablement teams, outpatient physiotherapy, falls prevention groups, national exercise referral services). The information will enable patients to ask the therapist they are working with or their GP about available services and what benefit they might offer, and at what stages they would be most beneficial, and to contact the services themselves for more information.
3) To enable them to work collaboratively with their therapist to set goals and monitor progress of their rehabilitation in order to improve the quality and the quantity of the physical and activities of daily living exercises they are performing.
4) To improve patients' self-efficacy
    a. To encourage the patient to set goals they want to achieve and to discuss them with their therapist.

b. To monitor the progress towards/attainment of these goals through keeping a diary of progress. This will provide feedback in the form of both self-reflection and reflection with the therapist. Feedback is recognised as an important component for improving self-efficacy [24].

5) To improve communication between hospital and community services, and between the patient and all the different professionals and services with which they come into contact during their rehabilitation.

6) To reduce patients' fear of falling by improving self-efficacy for avoiding falls/ exercising, and providing information about local falls prevention services

7) To signpost patients to local follow-on community programmes such as exercise referral and falls prevention services with contact details.

Therapists will be trained in each site to deliver the enhanced rehabilitation programme with fidelity. In addition, they will be provided on-going support with e-mails, newsletters and refresher events. New therapists will also be trained if others leave.

8.4 Assessment of Compliance with Trial Treatment/s

This will be considered as part of the process evaluation (Section 9.3.2).

8.5 Concomitant Medications/Treatments

As this is a pragmatic RCT comparing an enhanced rehabilitation programme with usual care, there will be no restrictions on concomitant medications or treatments. Details concerning medication and other treatment use will be collected by the CSRI questionnaire and transcribed into the trial database.

8.6 Who is Blinded to Allocations

Collection of outcome measures, including physical function measures, will be performed blind to treatment allocation by the RPSO. This is a pragmatic trial comparing two rehabilitation interventions, so it will not be possible to blind participants or their clinicians to treatment group allocation. We will include a perception of allocation form for the RPSO to complete, in order to monitor the level of blinding that was achieved for these researchers.

The RPSO will not be informed which group the patient participant has been randomised to and will not be present at any of the therapy sessions. When the RPSO visits the patient participant and carer participant, they will ask the participants before any assessments take place not to reveal trial allocation to the RPSO.

9 PARTICIPANT TIME LINE, ASSESSMENTS AND PROCEDURES

9.1 Schedule for Follow-up

Participant follow-up visits should take place at 17 and 52 weeks post randomisation

Procedures	Screening	Baseline / Randomisation *	Trial intervention**	17 weeks post randomisation Follow-up	Qualitative interviews	52weeks post randomisation Follow-up
Eligibility screening and consent						
Assessment of eligibility criteria	X					
Written and informed consent (patient / carer))	X					
Confirm consent		X	X	X	X	X
Randomisation		X				
Discharge data		X				
Outcome measurement - patient						
NEADL		X		X		X
HADS		X		X		X
AMTS		X		X		X
VAS hip pain intensity		X		X		X
FES-I		X		X		X
VASFoF		X		X		X
EQ-5D-3L		X		X		X
CSRI		X		X		X
Grip strength		X		X		X
SPPB				X		X
Outcome measurement - carer						
CSI		X		X		X
HADS		X		X		X
Trial Intervention**			X			
Qualitative interviews						
Re-affirm consent verbally specifically for qualitative phone interview. (patient / carer)					X	
Qualitative telephone interview					X	
Safety Event Reporting						
Monitoring of Adverse Events			X	X	X	X
Monitoring of Serious Adverse Events			X	X	X	X

* Randomisation and baseline should take place no later than 4 weeks after hip fracture repair surgery
** If randomised to intervention arm.

9.1.1 **Baseline**

Baseline should be recorded up-to 4 weeks after surgery, in line with timings for obtaining consent.

Participants: Data collection at baseline will include (but not limited to) type of hip fracture, co-morbid conditions, Date of surgery, type of surgery, prior living arrangements/place of residence.

Questionnaires administered at baseline will be NEADL, HADS, AMTS, VAS hip pain intensity, FES-I, VASFoF, EQ-5D-3L questionnaire, CSRI, Grip strength.

Carers: Care-giver CSI and care-giver HADS

9.1.2 **Discharge**

Date of discharge will be recorded, as will place of discharge and place of discharge.

9.1.3 **17 Week follow-up**

Follow-up visit should occur 17 weeks after randomisation.

Participants: Data collection will include (but not limited to) AEs and RSAEs.

Questionnaires administered will be NEADL, HADS, AMTS, VAS hip pain intensity, FES-I, VASFoF, EQ-5D-3L questionnaire, CSRI, Grip strength, SPPB.

Carers: Care-giver CSI and care-giver HADS.

9.1.4 **Qualitative interviews**

After the 17 week assessments; Semi-structured telephone interview with participants and carers by the qualitative researcher carrying out the process evaluation. Interviews will be audio recorded.

9.1.5 **52 Week follow-up**

Follow-up visit should occur 52 weeks after randomisation.

Participants: Data collection will be include (but not limited to) AEs and RSAEs.

Questionnaires administered will be NEADL, HADS, AMTS, VAS hip pain intensity, FES-I, VASFoF, EQ-5D-3L questionnaire, CSRI, Grip strength, SPPB.

Carers: Care-giver CSI and care-giver HADS.

9.2 Procedures for Assessing Safety

9.2.1 **Process for recording adverse events**

All adverse events will be recorded (across both arms) by researchers when they are made aware of the event by the patient, carer, the treating clinicians, or therapists, in accordance with the principles of 'Good Clinical Practice'. Adverse event reporting information will be included in the training given to the therapy teams delivering the intervention and they will be given Instructions on how to enter adverse events on to the trial database. The adverse event form will be completed by investigators at site who will complete information including the seriousness of the event and whether it is related to the intervention. All adverse events will be presented to the Independent Data and Safety Monitoring Committee (IDSMC) periodically. Trial- serious related events will be reported to the CTRC within 24 hours of sites becoming aware. They will also be reported to the IDSMC Chair person and the research ethics committee periodically.

9.3 Other Assessments

9.3.1 Health Economic Analysis

The enhanced rehabilitation programme will be fully costed (e.g., salary band of therapists, time spent with the patient conducting rehabilitation, costs of travel and costs of any additional equipment) from a public sector multiagency perspective including health and social care. Unit costs will be obtained from national sources of reference costs. Costs of health and social care services used by the participants will also be costed using national sources of reference costs [44,45]. The costs of service use and the cost of the intervention will be added together for use in a cost-utility analysis.

The EQ-5D -3L will be used to calculate QALYs over the 52-week trial period, using area under the curve method [41]. QALYs measure health gain by aggregating the number of years gained from a drug or health care intervention, weighted by the proportion that represents the relative value attached to a given health state (utility) [52].

A cost-utility analysis will be conducted to calculate a cost per QALY of the enhanced rehabilitation intervention. Differences in mean QALYs and service use costs between the groups will be calculated, and 95% Confidence Intervals around these differences produced. This cost per QALY generated will be compared to the NICE threshold range of £20,000 to £30,000 per QALY [53]. We will bootstrap differences in costs and outcomes (EQ-5D 3L) between the two groups, producing a 95% confidence interval around these differences.

9.3.2 Process Evaluation

The process evaluation of the FEMuR III trial will aim to examine the mechanisms and processes (i.e. the intervention theory) that explain the implementation and impacts of the enhanced rehabilitation programme. The process evaluation will help build a picture of how the FEMuR proposed programme is carried out in reality, and what factors shaped it. By carrying out a process evaluation it will be possible to identify if observed impacts are solely due to the enhanced rehabilitation programme, or if these impacts are a result of a number of external and internal variables that are closely linked to the environment and the context in which the programme takes place [56-59].
The specific objectives will be to:

- Refine the programme theory that was generated from the previous realist review when developing the intervention programme (MRC framework phase I). This will explain how the FEMuR enhanced rehabilitation programme is expected to work to generate outcomes amongst a complex patient group. This programme theory will also explain how the researchers envisage the intervention to reach its expected outcomes via identifying a set of tangible assumptions that will further be used to guide the analysis and synthesis of data.
- Investigate therapists' expectations and experience of implementation, identifying the actual practices, likely tailoring and interactions that took place within the trial setting. Also, investigate therapists' skill level, relevant training, previous experience and level of familiarity of working in this sector. Finally, investigate therapists learning over time and its potential impact on outcomes.
- Investigate the mechanisms driving and shaping the tailoring of the enhanced rehabilitation programme to individual patients and its possible impacts on outcomes.
- Investigate trial participants' experiences and views about their involvement in the FEMuR trial.
- Synthesise all data collected and link it to the explanation of trial findings in relation to the refined programme theory.

9.3.2.1 Process evaluation data collection

Qualitative interviews will be conducted with a purposive sample of 60 patient participants in each of the two trial arms and up-to 30 of their carers. Sampling will ensure engagement of trial participants

with different ages and functional impairment. Interviews will take place after the 17-week assessment. Participants will be asked to consent to being contacted after their 17-week follow-up in the main PISC form. Consent will be re-affirmed prior to a semi-structured telephone interview by the qualitative researcher carrying out the process evaluation. Interviews will be audio recorded.

Semi-structured in-depth interviews will be conducted with 40 therapists delivering the enhanced rehabilitation programme (four from 10-12 sites), and will explore implementation from the therapists' perspectives. Interviews are expected to last a maximum of an hour and will be audio recorded. Interviews will be carried out at two time points: midway through therapists' anticipated involvement in the trial, and at the end of their involvement. The interviews will be carried out over the telephone at a convenient date and time.

Therapists will be asked to record key reflections using a critical incident technique. Data will be collected in the form of 'critical incident reports' which follow a reflective cycle. Therapists will be asked to complete these reports throughout their involvement in FEMuR.

In order to describe the extra rehabilitation therapy sessions, the visiting therapist will record the length and content of each session on a case report form. In order to describe the usual rehabilitation programme provided by the NHS patients will have patient-held diaries for visiting therapists to complete in order to record the number, length and content of usual rehabilitation care. Also whenever possible, routinely collected electronic data that therapists complete on their Therapy Manager system or its equivalent will be collected. The NHS IT manager will extract activity data, and send the pseudonymised to the qualitative researcher identifiable only by participant trial ID (randomisation number). The following will be extracted from these treatment logs and from the electronic records:

- Randomisation number
- Date of extra session
- Whether the session was face to face or indirect
- Where the face to face session was held
- If the session was face to face, how much time was spent on different aspects such as, physical exercises, activities of daily living (ADL) practice, working on the workbook
- When the sessions were given in patient's recovery timeline

Data from these records will be used to monitor participant adherence (e.g. missed or cancelled appointments), and therapist adherence to the trial protocol. In addition, as part of the health economic data collection we will ask all patient participants to record health service and admissions data along with concomitant medication use on the CSRI collected at baseline and at 17 and 52 weeks' follow-up.

9.3.3 **Patient Transfer**

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating FEMuR III trial site and for this trial site to take over responsibility for the patient.. The CTRC should be notified in writing of patient transfers.

9.3.4 **Premature Discontinuation of Trial Intervention**

Patients may be withdrawn from treatment for any of the following reasons:

- The patient withdraws consent.
- Intercurrent illness preventing further treatment.
- Any change in the patient's condition that justifies the discontinuation of treatment in the clinician's opinion.

If a patient wishes to prematurely discontinue from trial intervention, sites should nevertheless explain the importance of remaining on trial follow-up.. Generally, follow-up will continue unless the patient explicitly also withdraws consent for follow-up (see section 9.3.5).

9.3.5 **Withdrawal from Trial Completely**

Patients or carer participants are free to withdraw consent at any time without providing a reason. Patients who wish to withdraw consent for the trial will have anonymised data collected up to the point of that withdrawal of consent included in the analyses. The patient will not contribute further data to the trial. Data up to the time of withdrawal will be included in the analyses in accordance with the Data Protection Act 2018.

9.4 Trial Closure

The end of the trial is defined to be the date on which data for all participants are locked and data entry privileges are withdrawn from the trial database. However, the trial may be closed prematurely by the Trial Steering Committee (TSC), on the recommendation of the Independent Data and Safety Monitoring Committee (IDSMC).

10 SAFETY REPORTING

All safety events will be recorded by researchers when they are made aware of the event by the patient, carer, the treating clinicians, or therapists, in accordance with the principles of GCP. Safety event reporting information will be included in the training given to the therapy teams delivering the intervention and they will be given copies of the safety event reporting forms and details of how to enter them on to the trial database or send to the CTRC.

AE reports and SAEs not related to the intervention will be entered on to the remote data entry system at follow-up visits. SAE reports related to the intervention will be completed and sent to the CTRC within 24 hours of becoming aware of the event.

Safety events will be captured on two separate forms: Adverse Events form for all non-serious events and SAEs not related to intervention and a Serious Adverse Events (SAE) form for serious events related to intervention. The SAE form will have two sections, the first is for the healthcare professional to complete at site who will complete information including the seriousness of the event and whether it is related to the trial and return to the CTRC trial manager. The trial manager will liaise with the Chief Investigator (or agreed delegate) who will complete the second part of the form, including an assessment of expectedness for related events.

All SAEs, along with the PI's assessment of whether it is related to the intervention and for related events the CI's assessment of whether or not it is expected, will be reported to the REC annually. All SAEs which are assessed as related and unexpected will be reported to the REC and Sponsor in an expedited manner.

10.1 Definitions

There are different categories of safety events.

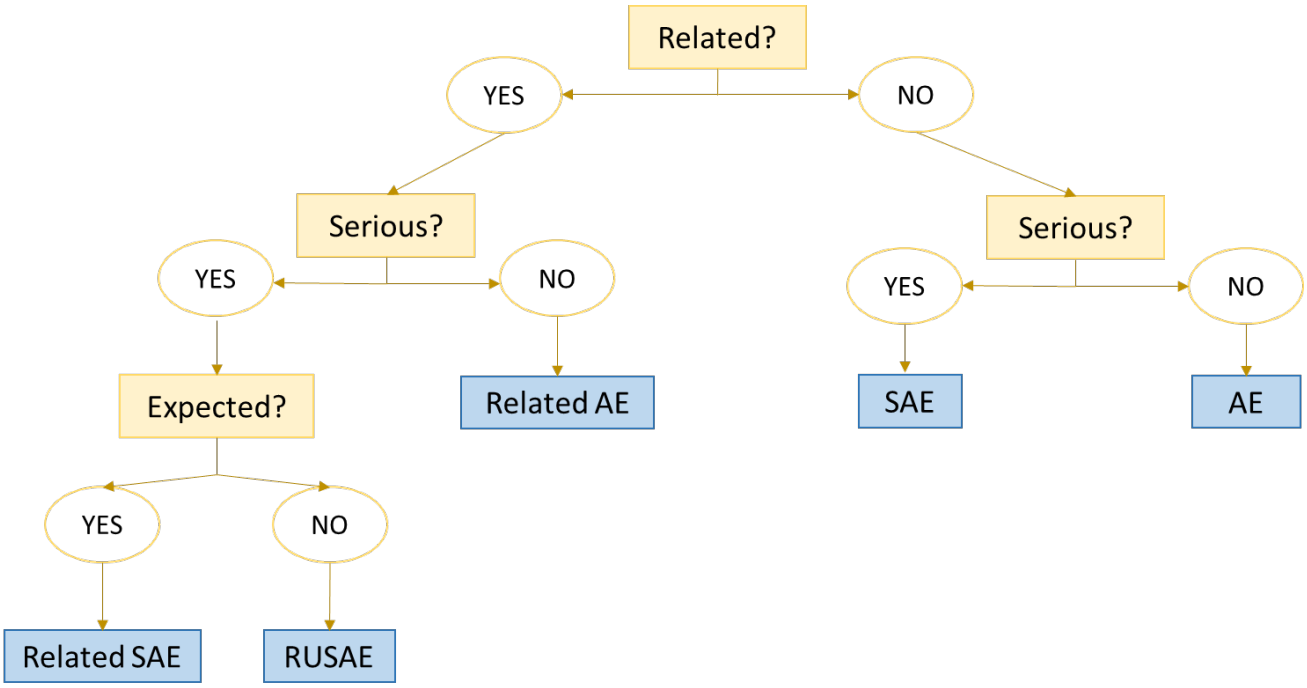
Adverse Event (AE)
An "Adverse Event" (AE) is any untoward medical occurrence in a participant, including events which are not necessarily caused by or related to the trial intervention. See section 10.2 for further guidance.

Related Adverse Event (related AE)
A "Related Adverse Event" (related AE) is an AE which has been assessed as having a causal relationship to the trial intervention (see section 10.5 below).

Serious Adverse Event (SAE)
A "Serious Adverse Event" is an AE which has been assessed as meeting the definition of "serious" (see section 10.3 below).

Related Serious Adverse Event (related SAE)
A "Related Serious Adverse Event" is an SAE which has been assessed as having a causal relationship to the study intervention (see section 10.5 below).

Related Unexpected Serious Adverse Event (RUSAE)
A "Related Unexpected Serious Adverse Event" is a related SAE which has been assessed as being unexpected (see section 10.6 below).



10.2 Notes on AE Inclusions and Exclusions

On this study AEs will include the following:

- Non-injurious falls;
- An exacerbation of a pre-existing illness;
- An increase in frequency or intensity of a pre-existing episodic condition;
- A condition (even though it may have been present prior to the start of the trial) detected after the start of the trial; and
- Continuous persistent disease or symptoms present at baseline that worsens during the trial.

The following will not be included as AEs:

- Medical or surgical procedures where the condition which leads to the procedure is the adverse event;
- Pre-existing disease or conditions present before treatment that do not worsen; and
- Overdose of medication without signs or symptoms.

10.3 Assessing “seriousness”

All safety events will be assessed for “seriousness”. The assessment of “seriousness” should be made by the investigator responsible for the care of the participant using the following criteria. Events meeting the below criteria will be classified as “serious” (i.e. SAEs, related SAEs / RUSAEs). A safety event will be assessed as “serious” if it:

- Results in death;
- Is life-threatening (refers to an event during which the participant was at risk of death at the time of the event; it does not refer to an event which might have caused death had it been more severe in nature);
- Is a fall that results in injury and repeat fractures;
- Requires hospitalisation or prolongation of existing hospitalisation;
- Results in persistent/significant disability or incapacity;

- Other important medical events that, based upon appropriate medical judgement, may jeopardise the participant and may require medical or surgical intervention.

10.4 Notes on Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below.
Regardless of the classification of a safety event as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

Mild: does not interfere with routine activities
Moderate: interferes with routine activities
Severe: impossible to perform routine activities

A distinction is drawn between serious and severe events. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 10.1, hence, a severe AE need not necessarily be a Serious Adverse Event.

10.5 Relationship to Trial Intervention

All safety events will be assessed for causality. The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in table Table 1: Definitions of Causality. If any doubt about the causality exists the local investigator should inform the CTRC who will notify the Chief Investigator.

Only events related to trial intervention should be reported, events related to trial participation but not necessarily the intervention do not need reporting,

Table 1: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur at the time, or as a consequence of, the rehabilitation intervention). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurred at the time, and may be a consequence of, the rehabilitation intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

In this study, only events which are assessed as "possibly", "probably" or "almost certainly" related will be classified as related events (i.e. related AEs / related SAEs / RUSAEs).

10.6 Assessing “expectedness”

The assessment of expectedness will be performed by the Chief Investigator (or agreed delegate), not by the site research team.

All safety events assessed as “serious” and “related” will be assessed as expected and classified as RUSAEs if they meet the following criteria:

- Repeat fall during therapy sessions
- Repeat fracture during therapy sessions
- Other accident of injury during therapy sessions

10.7 Follow-up after Adverse Events

All safety events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.
When reporting serious events (SAEs / related SAEs / RUSAEs) the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative);; ongoing at final follow-up; fatal or unknown.

10.8 Reporting Procedures

All safety events will be recorded and reported for each patient participant from the period of randomisation until their final 52 week follow-up assessment.

Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning safety event reporting should be directed to the CTRC in the first instance.

10.8.1 Non serious safety events (AEs / related AEs)

All such events, whether related or not, should be recorded on an Adverse Event Form and entered into the trial database (see section 10.2 for reportable events).

10.8.2 Serious safety events (SAEs / related SAEs / RUSAEs)

All serious events related to intervention, and whether expected or not should be recorded on an SAE form. The SAE form asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality. The responsible investigator should sign the causality of the event.

SAEs **related** to the intervention (related SAEs / RUSAEs) should be reported to the CTRC within 24 hours of the local site becoming aware of the event. SAEs that are **not related** to the intervention (SAEs) should be entered into the trial database at 17 or 52 weeks.

Local Principal Investigators should report any SAEs as required locally.

All serious events (SAEs / related SAEs / RUSAEs) will be reported annually to the REC and periodically to the IDSMC by the CTRC. Unexpected, related and serious events (RUSAEs) will also be reported in an expedited manner (15 days from CTRC being aware) to REC.

10.9 Responsibilities – Site Principal Investigator

The site Principal Investigator is responsible for recording and reporting to CTRC all safety events that are observed or reported during the trial, regardless of their relationship to the trial. All serious events related to intervention (SAEs / related SAEs / RUSAEs) must be reported immediately by the investigator to the CTU on an SAE form. All other adverse events and serious adverse events not related to intervention should be reported on the regular progress/follow-up reports.

Minimum information required for reporting

- Trial randomisation number
- Sponsor trial number
- One identifiable coded subject
- One identifiable reporter
- A causality assessment

I. The SAE form should be completed by a designated investigator, a physician named on the 'signature list and delegation of responsibilities log' as responsible for reporting serious safety events and making trial related medical decisions. The investigator should assess the event for the likelihood that it is a response to the trial intervention. In the absence of the designated investigator the form should be completed and signed by an alternative member of the research site trial team (as named on the delegation log) and submitted to the CTRC. As soon as possible thereafter the responsible investigator should check the SAE form, make amendments as appropriate, sign and re-send to the CTRC. The initial report shall be followed by detailed reports every 5 days until resolution.

II. When submitting a SAE to the CTRC research sites should also telephone the appropriate trial co-ordinator on telephone number **0151 795 8764** to advise that an SAE form has been submitted.

III. Send the SAE form by fax (within 24 hours or next working day) to the CTU:

Fax Number: 0151 795 8770

I. The responsible investigator must **notify** their R&D department of the event (as per standard local governance procedures).

II. The participant must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.

III. Follow-up information is noted on another SAE form by ticking the box marked 'follow-up' and returning to the CTRC as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.

IV. The patient **must** be identified by trial number, date of birth and initials only. The patient's name **should not** be used on any correspondence.

11 STATISTICAL CONSIDERATIONS

11.1 Method of Randomisation

Patient participants who give their informed consent will complete baseline processes and outcome measures before being individually randomised. The randomisation will be performed by the site team using 24 hour web based randomisation system to protect against subversion whilst ensuring that the trial maintains good balance to the allocation ratio of 1:1 both within each stratum and across the trial. Participants will be stratified by: (1) site and (2) gender. Randomisation will be requested by and will be archived by secure web access to the remote randomisation centre at the CTRC. This system will be set up, maintained and monitored independently of the trial statistician or other trial staff.

11.2 Sample Size calculation

The results from the phase II feasibility trial informed the sample size calculation. The adjusted mean difference in the primary outcome measure (NEADL) between the intervention and control group in the feasibility trial was three. Work completed by Wu, et al [30] has suggested that the minimum clinically significant difference is 2.4, so this has been used within the sample size calculation for this phase III RCT. A two-point score in the NEADL scale would equate to an improvement in function from being independent around the home to being able to use public transport or get in and out of a car. The adjusted mean difference between the groups in NEADL in the randomised feasibility trial had a standard deviation of 5.8. In this phase III RCT a more diverse sample would be expected with breadth in terms of geography, health care pathways, and populations, so a larger SD would be expected. Parker, et al. [31] used NEADL in a RCT comparing a rehabilitation intervention for older people in a day hospital compared with rehabilitation at home and found a SD of 10. Based on ANCOVA with alpha of 5% and 90% power to detect a difference of 2.4 (SD = 10, R^2 of covariate = 0.52) 352 patient participants would be required to complete the trial over both treatment groups. When considering the 79% retention rate, the trial would need to recruit 446 patient participants.

11.2.1 **Feasibility (attaining recruitment targets)**

The phase II trial has provided estimates of the recruitment and retention rates. In a nine-month period between June 2014 and March 2015, 593 patients with proximal femoral fracture were screened for eligibility, of which 266 (45%) were eligible. The main reason for ineligibility was lack of mental capacity (49%). Out of those eligible 193 (73%) were invited to participate and 62 (32% of the eligible population who were invited) agreed to participate. So to recruit 446 we would need to invite 1,394 who are eligible to participate and screen 3,097 patients with proximal femoral fracture. In order to do this we will aim to recruit 12 sites in six geographical locations: Merseyside, North Wales, South Wales, Nottingham, London and East Anglia and recruit participants over 14 months.

11.3 Analysis Plan

A fully documented Statistical Analysis Plan (SAP) will be written and agreed by CTRC statistical team and the IDSMC before data collection has been completed.

Descriptive statistics will be used such as recruitment and retention rates. Normally distributed outcome and process measure scores will be reported as mean scores with their standard deviations at baseline and at follow-up after 17 and 52 weeks. Medians and interquartile ranges will be used for skewed outcome measure data. Differences between hospitals will be presented for all outcomes.

Analysis will be conducted on an intention to treat basis, blind to treatment allocation. The main analysis for primary and continuous secondary outcomes at 17 and 52 weeks will be an analysis of covariance (ANCOVA) adjusted for baseline score, allocation group and stratification variables. The aim is to minimise missing data; however, predictors of missing data will be investigated using

regression models and any significant predictors will be considered for inclusion in the models. Multiple imputation will be employed to address missing scores where appropriate. Analysis of complete case data will be completed as a sensitivity analysis to establish the sensitivity of the treatment effect estimates to the missing data. In addition, given the two assessment points at 17 and 52 weeks, we will carry out a sensitivity analysis using a joint modelling approach to check whether there is any difference in outcome (here the longitudinal outcome rather than the outcome at 17 weeks or 52 weeks alone) between the randomised arms adjusted for dropout or missingness. All treatment effect estimates will be presented with 95% confidence intervals. Sub-group analysis will be planned *a priori* and will be included in the statistical analysis plan. It will include a Complier Average Causal Effect (CACE) analysis based on a number of characteristics decided *a priori*, which will include variables such as the number of therapy sessions received.

11.4 Procedures for Assessing Effectiveness

Effectiveness will be determined comparing patient-completed NEADL scale scores at 52 week follow-up between the two intervention groups.
Nottingham Extended Activities of Daily Living (NEADL) Scale[35]
This is a patient-completed outcome measure of activities of daily living from the previous 4 weeks which has evidence of validity in stroke patients. The NEADL is a record of actual activity rather than capability, scoring patients in the areas of mobility, kitchen, domestic and leisure activities. A higher score indicates a greater level of independence. When assessed at baseline, it will assess the participant's functional capacity prior to hip fracture. When NEADL is administered the patient will be asked to recall the 4 weeks prior to hip fracture and not 4 weeks prior to completing this questionnaire. It will also be used at the 17 and 52-week follow-up assessment to assess the degree of functional recovery. The score range is 0 to 66 with higher scores indicating greater independence.

11.5 Secondary Objectives of Cost-Effectiveness and Mechanisms/Processes

Patient completed measures - secondary outcome

Hospital Anxiety and Depression Scale (HADS)[36]
This is a patient-completed outcome measure of anxiety and depression. It is designed to measure anxiety and depression in patients with physical health problems. It has seven items related to common symptoms of anxiety and seven for depression. Patients are asked whether they experience the symptom definitely, sometimes, not much or not at all. The HADS was designed for use in the hospital setting but has been used successfully with the general population. This measure will be used at baseline and at the 17 and 52 week follow-up assessment. The two sub-scales have a range of 0 to 21 with higher scores indicating increased anxiety or depression.

Process measures

Abbreviated Mental Test Score (AMTS)[33].
The AMTS is a test with evidence of validity that is widely used in clinical and research settings in the UK for detecting and monitoring cognitive impairment. This will be used as a baseline description of the level of cognition. It is brief (ten items) and recommended for cognitive screening in acute settings in the Alzheimer's Society (2013) tool-kit[34] 'Helping you to assess cognition: a practical toolkit for clinicians'. It is generally considered to be easily administered and well tolerated by raters and subjects. This measure will be used at baseline and at the 17 and 52 week follow-up assessments. The score range is 0 to 10 with higher scores indicating worse cognitive function.

Visual Analogue Scale (VAS) for hip pain intensity[37]
This is a patient-completed VAS of current hip pain intensity. Hip pain following surgery is an important factor affecting rehabilitation and will be measured at baseline and at the 17 and 52 week follow-up assessment. We have chosen a VAS as there is evidence of validity compared with the Oxford Hip Score whilst being simpler and quicker to complete, thus reducing the burden on patients. The range is 0 to 10 on a segmented line.

Falls Efficacy Scale - International (FES-I) (self efficacy)[38,39]
The FES-I measures how concerned a patient is about falling when performing activities of daily living both inside and outside of the home. The scale details 16 activities which the patient must rate from 1 (not at all concerned) to 4 (very concerned) with regards to how concerned they would be about falling if they performed the activity. The range is 16 to 64 with higher scores indicating a greater fear of falling. The FES-I has been used successfully in older patients both without and with mild cognitive impairment and will be used to measure fear of falling in our trial at baseline, 17 and 52 week follow-up.

Visual Analogue Score - Fear of Falling (VASFoF)[40]
This is a patient-completed VAS for fear of falling. A VAS is useful as it is easy to administer and brief. The range is 0 to 10 on a segmented line with higher scores indicating greater fear of falling. It has previously been used in older adults with and without cognitive impairment with good results and will be used to measure fear of falling in our trial at baseline, 17 and 52 week follow-up.

Grip strength[46]
This is an objective measure of physical function that will be administered in a standardised manner by the researcher administering the patient-completed questionnaires. Grip strength correlates well with general fitness and muscle strength relating to physical function[47,48]. It is also a more appropriate measure for use at baseline, as performing other physical assessments may carry risk to patients at this time point or would be likely to primarily reflect post-operative pain and not overall function. Grip strength will be measured at baseline and at the 17 and 52 week follow-up assessments.

Short Physical Performance Battery (SPPB)[49,50]
This is a short series of physical function tests which assess lower limb function in terms of balance, gait, strength and endurance. The tests involve: examining the ability to stand with feet together in the side-by-side, semi-tandem and tandem positions; measuring the time to walk 8 feet (2.5m) and the time to rise from a chair and return to the seated position five times. Each test and a summary performance scale obtained by summing the categorical ranking on each test (0-12) were strongly associated with self-reported disability and were independent predictors of short-term mortality and nursing home admission. This was found even at the high end of the functional spectrum in those reporting almost no disability. This battery of tests was designed for use in people's homes and will be administered by the researcher at the 17 and 52 week follow-up assessments.

Health economic measures

EuroQol EQ-5D-3L (three levels)[41]
This is a patient-completed index of health-related quality of life, which gives a weight to different health states. It consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each has three possible responses. The responses record three levels of severity (no problems, /moderate problems, or severe problems) which is then converted to a health utility weight using UK norms. It also has a VAS ranging from 0 to 100 where the participant draws a line on the scale to rate their health state today. It will be used at baseline and at the 17 and 52 week follow-up assessments, and allows the calculation of quality-adjusted life years (QALY) using the area under the curve method which will be used as part of the economic analysis[42].

Client service receipt inventory (CSRI)[43]

The CSRI is a questionnaire for collecting retrospective information about trial participants' use of health and social care services, including voluntary services (e.g. charity services) and the components of the rehabilitation programme. This information will be combined with national sources of reference unit costs[44,45] in order to calculate health and social care service costs for the economic evaluation. It will be used at baseline and at the 17 and 52 week follow-up assessments as part of the economic analysis. A reduced version of the CSRI will be used at baseline to reduce participant burden as participants are recovering from hip fracture surgery.

Carer completed measure - secondary outcome

Caregiver Strain Index (CSI)[51]

Carers who have been recruited into the trial will be asked to complete this measure. It is a 13-item tool that measures strain related to care provision. There is at least one item for each of the following major domains: employment, financial, physical, social and time. Positive responses to seven or more items indicate a greater level of strain. It can be used to assess individuals of any age who have assumed the role of caregiver for an adult aged 60 or over. It will be completed at baseline and at the 17 and 52 week follow-up. The range is 0 to 13 with a higher score indicating greater strain.

Hospital Anxiety and Depression Scale (HADS)[36]

Carers will be asked to complete the HADS as a measure of their anxiety and depression at baseline and at the 17 and 52 week follow-up.

12 REGULATORY AND ETHICAL APPROVALS

12.1 Statement of Compliance

Statement of compliance: The trial will be carried out in accordance with:

- The World Medical Association Declaration of Helsinki (1996) and the following updates Edinburgh (2000), Seoul (2008) and Fortaleza (2013)
- CTRC Standard Operating Procedures
- Principles of Good Clinical Practice
- The template content is structured consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013)
- UK policy framework for health and social care research

12.2 Ethical Considerations

The trial will abide by the principles of the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996).

Potential ethical issues include informed consent where potential patient and carer participants will be identified by NHS clinicians providing their usual care and will avoid any coercion. Lack of mental capacity to give informed consent will be an exclusion criterion. Clinical equipoise exists for this trial because there is no evidence that the intervention improves patient outcome, so the trial team believe it is acceptable to randomise patients to the two treatment groups. The enhanced rehabilitation intervention is low risk as it consists of a workbook, diary and extra therapist time. The workbook does include examples of physical activities and exercises, and encourages patients to think about what they would like to achieve in consultation with their therapist, who will assess whether the goal is suitable and achievable. We will record safety events and take advice from the Independent Data and Safety Monitoring Committee (IDSMC) regarding the frequency of these, especially those deemed related to the intervention. The control group poses no additional risk to participants randomised to the control group as they will receive care as usual. The research officers will not only administer patient reported questionnaires at 17 and 52 week follow-up to maximise response rate, but also the SPPB. This has been designed to be administered in patients' homes and tests balance, gait speed and the ability to rise from a chair. The research officers will receive training in how to administer this safely, and will follow a lone worker policy.

Many of the frail elderly people that fracture their hip have cognitive impairment. Those who lack mental capacity to give informed consent are excluded from this RCT, however others with mild cognitive impairment or in the early stages of dementia are still eligible. The assessment of mental capacity is a clinical assessment which will be performed by clinicians on the orthopaedic wards. The following questions will need to be considered:

- Is the person able to understand the information relevant to the decision (to participate or not)?
- Is the person able to retain the information provided (which can be determined by a simple question of recall)?
- Can the person use or weigh that information as part of the process of making the decision (which can be assessed by inquiring of the person's understanding or potential options for participation)?
- Is the patient able to communicate his/her decision?

If the question is no to one or more of these questions, the patient will not be approached as they do not meet the eligibility criteria for inclusion in the trial. Also although the AMTS will not be used to determine eligibility, if the person has a low score then the clinician will be asked to re-assess capacity.

Some of the potential participants will initially be ineligible because of a temporary delirium. These people can be re-assessed several days later when the delirium has settled. The research team can maintain contact even if the patient is transferred to another ward for in-patient rehabilitation, or discharged home.

The mental capacity of participants may change. If the participant no longer has capacity when arranging a follow-up visit, no further data can be collected until the participant has been assessed as regaining capacity. Baseline data and other data collected up to that point will be used in the analysis.

Many of the participants can be classified as vulnerable adults. The clinicians and researchers in contact with them will have received statutory protection of vulnerable adults (POVA) training. This will be reported on a trial training log. A mechanism of immediate risk assessment and onward referral to appropriate authorities and police has been developed within the framework of the Human Rights Act 1998 and Data Protection Act 2018 if abuse or neglect is suspected, observed or disclosed by the participants.

12.3 Ethical Approval

Submission for NHS research ethics and NHS local governance approvals will be performed in the four months prior to the trial start date. All trial documentation, including PISC forms, template GP letters, and questionnaires will be submitted for approval. To conform to the Data Protection Act and Freedom of Information Act, all data will be pesudonymised and stored securely. No published material will contain patient identifying information.

12.4 Trial Discontinuation

In the event that the trial is discontinued all participants will complete their rehabilitation treatments as randomised. No further patients will receive the enhanced rehabilitation programme.

13 DATA MANAGEMENT AND TRIAL MONITORING

Details of the monitoring to be carried out for the FEMuR III trial are included in the FEMuR III Trial Monitoring Plan. Trial Oversight Committees related to the monitoring of the trial are detailed in section 15.

13.1 Source Documents

Source data will be the hospital written and electronic medical records, community electronic and written records, audio-recordings and transcripts of qualitative interviews. The CRF will be considered the source document for data such as questionnaires where no prior record exists and which is recorded directly in the eCRF. Data collected (questionnaires, AEs and other data) will be transcribed into the remote electronic data capture system by the RPSO.

Date(s) of conducting informed consent process including date of provision of patient information, randomisation number and the fact that the patient is participating in a clinical trial (including possible treatment arms) will be added to the patient's medical record chronologically.

13.2 Data Capture Methods

For this trial quantitative data collected at each of the time points will be entered into a web-based data management system allowing controlled access to data by all sites with a full audit trail. The source electronic Case Report Forms (e-CRFs) in the web-based data management system is the primary data collection instrument for this trial and will have the design, format, derivation and validations used for each type of question documented in the Coding Specification.

The database will contain automatic validations and restrictions at the point of data entry to minimise data inconsistencies. A Data Management Plan (DMP) will be written and it will cover processes for receipt (SAE forms, consent forms), processing and storage of data.

The data will be reviewed periodically and data queries will be raised electronically on any missing, inconsistent or out of range data recorded in the database.

The data captured will be stored in a database running on servers maintained by the University of Liverpool. Access to the complete database will be limited to the core team members of the project involved in data management, data cleaning and analysis.

Audio recordings of qualitative data from interviews will be collected by the qualitative researcher and stored at the University of Liverpool.

Additional health service use data obtained from primary and secondary care records will be recorded electronically on encrypted laptop computers or collected by NHS staff on secure computers and anonymised in an electronic data set that is ready for secure transfer to the CTRC.

13.2.1 **Data processing**

All data requested on the eCRF must be entered. All missing data (not entered) will be queried. The database will be designed to allow sites to state whether a data item is not known or not applicable. Personnel at participating sites who are delegated the responsibility for entering data will be assigned unique usernames and passwords for the electronic system. An audit trial of all data entered into the system will be maintained which will log details of any changes made to the data. Data from patient completed questionnaires and demographic data at baseline, 17 weeks and 52 weeks follow-up assessments will be entered onto laptop computers by the RPSO administering the questionnaires. The original patient completed questionnaires will be stored securely at the site.

13.2.2 **Central Monitoring**

Data entered into the online system will be checked for missing or unusual values (range checks) and checked for consistency. Any suspect data will be queried within the online system. Data queries will be raised within the system by CTRC data management. Sites should respond to the queries providing an explanation/ resolution to the discrepancies and update the database where applicable. This process will take place within the electronic system and paper CRFs. There are a number of monitoring features in place at the CTRC to ensure reliability and validity of the trial data, to be detailed in the trial monitoring plan.

Screening and recruitment rates will be monitored by the Trial Management Group to identify and barriers to recruitment and discuss options to remove barriers if appropriate.

Completion and return rate of consent forms will be monitored at the CTRC to ensure valid consent has been obtained and consent forms are returned within the timeframes of the Trial Monitoring Plan.

13.2.3 **Clinical Site Monitoring**

In order to perform their role effectively, the trial coordinator, data manager (or monitor) and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient records, laboratory reports, appointment books, etc. Since this affects the patient's confidentiality, this fact is included on the Parent Information Sheet and Informed Consent Form. During a site monitoring visit the trial coordinator, data manager (or monitor) and persons involved in Quality Assurance and Inspection may also review the Investigator Site File (ISF) to ensure all essential documents are present and the ISF is being maintained appropriately.

13.3 Confidentiality

Individual patient participant medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

The CTRC will be undertaking activities requiring the transfer of identifiable data for both patient and carer participants.

- Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed PISCs being supplied to the CTU by recruiting sites, which requires that name data will be transferred to the CTU.
- The RPSO will be responsible for co-ordinating the follow-up assessment of trial participants following discharge from hospital, and therefore will be required to receive contact details including name, address and telephone details.

This transfer of direct identifiers data is disclosed in the PISCs. The CTRC will preserve the confidentiality of participants taking part in the trial and The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

13.4 Quality Assurance and Control

The Trial Coordinator at the CTRC will verify appropriate approvals are in place prior to initiation of a site and the relevant personnel have attended trial specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at CTRC and the individual site.

The Trial Management Group (TMG) will determine the minimum key staff required to be recorded on the delegation log in order for the site to be initiated. The TMG will also monitor the screening, randomisation and consent rates between sites.

The trial will be conducted in accordance with procedures identified in the protocol. Independent oversight of the trial will be provided by the Data and Safety Monitoring Committee and independent members of the Trial Steering Committee.

The PI and other key staff from each site will attend site initiation training, coordinated by the CTRC, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol. Site staff will receive an on-site training visit by the trial co-ordinator and CI (if available) before green light to begin recruitment is give. The site training visit will consist of a review of the trial protocol, recruitment, consent, randomisation, follow-up, trial procedures, safety event reporting, intervention, trial arrangements, data protection and data handling.

Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. The process for consent, recruitment and randomisation will be evaluated for compliance with the protocol. Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan;

Full details of data evaluation can be found in the trial Data Management Plan

13.5 Records Retention

Trial records will be archived for a maximum of 25 following the End of Trial (see section 9.4 above).

The PI at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Site File, until the CTRC informs the investigator that the documents are no longer to be retained.

The PI is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities).

The PI is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The CTRC undertakes to store originally completed CRFs for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only. The CTRC will archive the documents in compliance with the principles of GCP. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to secure premises where unique reference numbers will be applied to enable confidentiality, tracking and retrieval.

14 INDEMNITY

The University of Liverpool holds insurance against claims from participants for harm caused by their participation in this clinical trial. Participants may be able to claim compensation if they can prove that the University of Liverpool has been negligent. However, if this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. Sponsor, University of Liverpool, does not accept liability for any breach in the hospital's duty of care, or any negligence of the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

15 ROLES AND RESPONSIBILITIES

15.1 Role of Trial Sponsor and Trial Funder

The sponsor will be the University of Liverpool, who will assume overall responsibility for the initiation and management of the trial. The day-to-day coordination of the study will be delegated to the CTRC.

The sponsor will ensure that clear agreements are reached, documented and carried out, respecting the dignity, rights, safety and wellbeing of participants and the relationship with healthcare professionals. This will provide for proper design, management, initiation, conduct, monitoring, data collection, data analysis, data protection, financing and reporting of this trial meeting appropriate scientific, legal and regulatory standards. The responsibility for design, conduct, management, data analysis, data interpretation, manuscript writing and dissemination of results is delegated to the TMG.

The funder is the NIHR HTA programme. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health.

15.2 Funding and Support in Kind

Funder(s)	**Financial and Non-financial Support Given**	**Role**
NIHR HTA programme	Financial funding	The funders will ensure there is proper use of the funds they have allocated to provide value for money. The funders assure the quality of the trial, taking the lead in establishing that the research proposal is worthwhile, of high scientific quality, has an appropriate research infrastructure with expert clinical trial management, has the capacity to comply with the principles of GCP and represents good value for money.

15.3 Trial Committees

15.3.1 **Trial Management Group (TMG)**

A TMG will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the CTRC. The TMG will be responsible for the day-to-day running and management of the trial and will meet approximately 3 times a year. Refer to the TMG terms of reference and trial oversight committee membership document for further details.

15.3.2 **Trial Steering Committee (TSC)**

The Trial Steering Committee will consist of an independent chairperson, 2 independent experts in the field of hip fractures and rehabilitation and an independent biostatistician. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The

ultimate decision for the continuation of the trial lies with the TSC. Refer to the TSC terms of reference and trial oversight committee membership document for further details.

15.3.3 **Independent Data and Safety Monitoring Committee (IDSMC)**

The independent Data and Safety Monitoring Committee (IDSMC) consists of an independent chairperson, plus 2 independent members who are experts in the field of hip fractures and rehabilitation.

The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will first convene prior to the start of recruitment and will then define frequency of subsequent meetings (at least annually). Details of the interim analysis and monitoring are provided in section 11 and 13.

The IDSMC will provide a recommendation to the TSC concerning the continuation of the trial. Refer to the IDSMC charter and trial oversight committee membership document for further details.

15.4 Protocol Contributors

Name	Affiliations	Contribution to protocol
Nefyn H Williams	Department of Health Services Research, University of Liverpool	Chief Investigator
Helen Hickey	Clinical Trials Research Centre University of Liverpool Institute of Child Health Alder Hey Children's NHS Foundation Trust Liverpool	Head of Trial Management
Ben Hardwick	Clinical Trials Research Centre University of Liverpool Institute of Child Health Alder Hey Children's NHS Foundation Trust Liverpool	Supervising Trial Manager
Susanna Dodd	Clinical Trials Research Centre University of Liverpool Institute of Child Health Alder Hey Children's NHS Foundation Trust Liverpool	Senior Statistician
Clare Jackson	Clinical Trials Research Centre University of Liverpool Institute of Child Health Alder Hey Children's NHS Foundation Trust Liverpool	Senior Data Manager
Lola Howard	Clinical Trials Research Centre University of Liverpool Institute of Child Health Alder Hey Children's NHS Foundation Trust Liverpool	Trial Co-ordinator
Jo Charles	Site for Health Economics and	Health Economist

	Medicines' Evaluation, Bangor University	
Toby Smith	NDORMS, University of Oxford	Lead applicant for Oxford University
Monica Busse-Morris	School of Medicine, Cardiff University	Lead applicant for Cardiff University
Janine Bates	SEWTU, Cardiff	Trial manager SEWTU

16 PUBLICATION AND DISSEMINATION

16.1 Publication Policy

The results from different sites will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the TMG.

The TMG will form the basis of the Writing Committee and advise on the nature of publications and will develop a publication strategy. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants, and if there are named authors, these should include the trial's Chief Investigator, Statistician(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.

The members of the TSC and IDSMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

16.1.1 **Authorship**

Contributors to all four of (i) the design, conduct, data analysis and interpretation, (ii) writing, (iii) manuscript approval and (iv) accountability for the integrity of the work will, depending on their contribution and journal requirements, be included by name at the manuscript head.

16.2 Dissemination to Key Stakeholders

Results from the trial will be presented at scientific meetings where interested doctors, therapists, nurses and health service commissioners will be present. We will write a final report and papers to international journals. The results will be distributed to policy makers, advisory groups, professional bodies and patient support groups.

The results will be disseminated regardless of the magnitude or direction of effect.

16.3 Data Sharing

Data sharing requests will need to be reviewed and approved by the CI, sponsor and CTRC. All quantitative data will be accompanied by the relevant codebook. The request and the data set provided to which member will be recorded and saved in respective folders named after the member.

17 CHRONOLOGY OF PROTOCOL AMENDMENTS

17.1 Version 1.0 (27/07/2018)

Original Approved version.

18 REFERENCES

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19 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

Patient and carer participant information sheets and consent forms
GP Letter
Questionnaires
Participating sites

20 APPENDICES